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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/851,071	05/08/2001	Ann Marie Schmidt	0575/55424-Z/JPW/SHS/MVM	3248

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John P. White  
Cooper & Dunham LLP  
1185 Avenue of the Americas  
New York, NY 10036

EXAMINER

KAUSHAL, SUMESH

ART UNIT	PAPER NUMBER
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1636

DATE MAILED: 07/28/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/851,071

Applicant(s)

SCHMIDT ET AL.

Examiner

Sumesh Kaushal Ph.D.

Art Unit

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --  
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 01 June 2004.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 17, 19, 20, 34 and 35 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 17, 19, 20, 34 and 35 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 08 May 2001 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)  
Paper No(s)/Mail Date \_\_\_\_\_.
- 4) ☐ Interview Summary (PTO-413)  
Paper No(s)/Mail Date. \_\_\_\_\_.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: \_\_\_\_\_.

**DETAILED ACTION**

*Claims 1-16, 18, 21-33 and 36-39 are canceled.*

*Claims 17, 19-20 and 34-35 are pending and are examined in this office action.*

*Applicants are required to follow Amendment Practice under revised 37 CFR §1.121. The fax phone numbers for the organization where this application or proceeding is assigned is 703-872-9306.*

**Continued Examination Under 37 CFR 1.114**

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 06/01/04 has been entered.

Applicant's arguments with respect to claims 17, 19-20, and 34-35 have been considered but are moot in view of the new ground(s) of rejection.

**Claim Rejections - 35 USC § 102**

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 17, 19-20 and 34 are rejected under 35 U.S.C. 102(b) as being anticipated by Gehlsen et al (JCB 106:925-930, 1988).

The instant invention as claimed is drawn to a method for evaluating the ability of an agent to inhibit tumor cell spreading, wherein the agent inhibit the interaction between a tumor cell and an extracellular matrix molecule.

Gehlsen teaches inhibition of in-vitro tumor cell invasion by Arg-Gly-Asp-containing synthetic peptides. Regarding claim 17(a) the cited art teaches that for the invasion assays the synthetic candidate polypeptides were dissolved in DME (cell culture media) with 2% FBS, 0.1% Gentamycin and 10mM Hepes buffer. The cited art further teaches that for cell attachment assay the peptides were dissolved in same media except the serum was omitted (page 926, col.1 para.4). The cited art further teaches that tumor cells were cultured in DME culture media supplemented with 10%FBS and 0.1% gentamycin (page 926, col.1 para.1). The cited art further teaches the attachment of purified extracellular matrixes (i.e. Fibronectin and Vitronectin) to the polystyrene culture dishes (page 926, col.1 para. 2). Regarding claim 17(b) and (c) the cited art teaches evaluation of invasiveness of tumor cells using a membrane invasion culture system (MICS). The tumor cells (A375 melanoma, RuGli glioblastoma) were preincubated and cultured into upper compartment of the MICS chamber followed by addition of peptide-containing medium (page 926, col.2 para.1, fig-1). Regarding claim 17(d) the cited art teaches that at specific time intervals after the addition of the candidate peptide the medium from upper and lower compartments of the chamber was removed and total number of cells that passed through the membrane was evaluated (page 926, col.2 para.1, fig-1). The cited art further teaches microscopic evaluation of spreading of tumor cells in the presence of absence of candidate agents (page 926, col.2 para.2). Regarding claims 19-20 the cited art teaches metastatic melanoma cells (A375m, A375P) and RuGli glioblastoma cells (page 926, clo.2 para.3). Regarding claim 34 the cited art teaches that the MICS membrane invasion culture system used herein comprises a human amniotic basement membrane (denuded of cells), which express extracellular matrix proteins laminin, type IV collagen, fibronectin and vitronectin (page 929, col.1 para.1-3, col.2 para. 4, page 925, col.1-2). In addition the cited art further

teaches the attachment of purified extracellular matrixes (i.e. Fibronectin and Vitronectin) to the polystyrene culture dishes (page 926, col.1 para. 2). Thus the cited art clearly anticipate the invention as claimed.

### ***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gehlsen et al (JCB 106:925-930, 1988) as applied to claims 17, 19-20 and 34 above, and further in view of Seftor et al (PNAS 89:1557-1561, 1992, *ref of record*).

The invention as claimed is drawn to a method for evaluating the ability of an agent to inhibit tumor cell spreading, wherein the agent inhibits the interaction between tumor cell and an extra cellular matrix molecule. The scope of candidate agent encompasses a molecule, which inhibits the interaction of tumor cell with an extra cellular matrix, wherein the extracellular matrix is an  $\alpha V\beta 3$ ,  $\alpha V\beta 5$  or  $\alpha I\beta 1$  integrin.

Gehlsen teaches inhibition of in-vitro tumor cell invasion by Arg-Gly-Asp-containing synthetic peptides. Regarding claim 17(a) the cited art teaches that for the invasion assays the synthetic candidate polypeptides were dissolved in DME (cell culture media) with 2% FBS, 0.1% Gentamycin and 10mM Hepes buffer. The cited art further teaches that for cell attachment assay the peptides were dissolved in same media except the serum was omitted (page 926, col.1 para.4). The cited art further teaches that tumor cells were cultured in DME culture media supplemented with 10%FBS and 0.1% gentamycin (page 926, col.1 para.1). The cited art further teaches the attachment of purified extracellular matrixes (i.e. Fibronectin and Vitronectin) to the

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polystyrene culture dishes (page 926, col.1 para. 2). Regarding claim 17(b) and (c) the cited art teaches evaluation of invasiveness of tumor cells using a membrane invasion culture system (MICS). The tumor cells (A375 melanoma, RuGli glioblastoma) were preincubated and cultured into upper compartment of the MICS chamber followed by addition of peptide-containing medium (page 926, col.2 para.1, fig-1). Regarding claim 17(d) the cited art teaches that at specific time intervals after the addition of the candidate peptide the medium from upper and lower compartments of the chamber was removed and total number of cells that passed through the membrane was evaluated (page 926, col.2 para.1, fig-1). The cited art further teaches microscopic evaluation of spreading of tumor cells in the presence or absence of candidate agents (page 926, col.2 para.2). Regarding claims 19-20 the cited art teaches metastatic melanoma cells (A375m, A375P) and RuGli glioblastoma cells (page 926, col.2 para.3). Regarding claim 34 the cited art teaches that the MICS membrane invasion culture system used herein comprises a human amniotic basement membrane (denuded of cells), which express extracellular matrix proteins laminin, type IV collagen, fibronectin and vitronectin (page 929, col.1 para.1-3, col.2 para. 4, page 925, col.1-2). In addition the cited art further teaches the attachment of purified extracellular matrixes (i.e. Fibronectin and Vitronectin) to the polystyrene culture dishes (page 926, col.1 para. 2)

However, Gehlsen does not specifically teach the interaction of an agent that inhibit tumor cell spreading by inhibiting interaction between tumor cells and integrins  $\alpha V\beta 3$ ,  $\alpha V\beta 5$  or  $\alpha I\beta 1$  integrin.

Seftor teaches a method for evaluating the ability of an agent to inhibit tumor invasion using an in-vitro invasion assay in context with  $\alpha V\beta 3$  integrin (page 1557 abstract). Regarding claim 35 the cited art explored the relationship between the function and expression of  $\alpha V\beta 3$  integrin in A375M human melanoma cells and ability of these cells to invade in-vitro by modulating  $\alpha V\beta 3$  integrin with either antibodies or its ligand vitronectin (page 1557 col.2 para.1). The cited art teaches membrane invasion culture system (MICS), wherein the assay was performed on the polycarbonate filter containing 10 $\mu$ m pores coated with Matrigel (extracellular matrix component complex).

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The cited art further teaches that adhesion of human melanoma cells to vitronectin, fibronectin and laminin in the presence of antibodies to various anti-integrin subunits was done according to *Gehlsen et al* specifically (page 1558, col.1 para.3). The cited art further teaches the determination of invasive potential of the treated and untreated tumor cells (page 1558, col.1 para.2, page 1559, fig-3). The cited art teaches that pretreatment of tumor cells with soluble vitronectin prior to assay resulted in increase in tumor cell invasion (page 1559, col.2 para.2). The cited art further teaches the A375M human melanoma cells express the  $\alpha V\beta 3$  integrin, wherein the  $\alpha V\beta 3$  integrin play an active role in mediating the attachment of these cells to their substratum. The cited art further teaches that  $\alpha V\beta 3$  integrin is known to bind to number of Arg-Gly-Asp (RGD) containing proteins such as vitronectin, laminin and entacti/nidogen (page 1559, col.2 para.5).

Thus it would have been obvious to one ordinary skill in the art at the time the instant invention was made to modify the invention of Gehlsen by specifically evaluating the ability of an agent that inhibits the interaction between a tumor cells and an intergrin in view of Seftor. One would have been motivated to do so identify candidate agents to inhibit tumor metastasis. One would have a reasonable expectation of success, since evaluation of a candidate compound that inhibit extracellular-matrix/tumor-cell interaction using a tumor attachment assay or a tumor invasion assays had been routine in the art the time the instant invention was made. Thus the invention as claimed is *prima facie* obvious in view of cited prior art of record.

### **Conclusion**

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sumesh Kaushal Ph.D. whose telephone number is

571-272-0769. The examiner can normally be reached on Mon-Fri. from 9AM-5PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yucel Irem Ph.D. can be reached on 571-272-0781.

*Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.*

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199. The fax phone number for the organization where this application or proceeding is assigned is **703-872-9306**.

Sumesh Kaushal  
Examiner GAU 1636



**SUMESH KAUSHAL**  
**PATENT EXAMINER**